SOX2 O-GlcNAcylation alters its protein-protein interactions and genomic occupancy to modulate gene expression in pluripotent cells.

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Authors: Samuel A Myers, Sailaja Peddada, Nilanjana Chatterjee, Tara Friedrich, Kiichrio Tomoda, Gregor Krings, Sean Thomas, Jason Maynard, Michael Broeker, Matthew Thomson, Katherine Pollard, Shinya Yamanaka, Alma L Burlingame, Barbara Panning

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Public Summary:
SOX2 is a transcription factor that is central to the identity of many cell types, including embryonic stem cells (ESCs), neural stem cells and pancreatic precursors. In each cell type SOX2 directs expression of a set of genes unique to that cell type. One mechanism by which the same transcription factor can mediate very different outputs is regulation by post-translational modifications (PTMs) - chemical changes to the protein that affect its ability to interact with other proteins or bind to DNA. We characterized the PTM profile of SOX2 in ESCs and differentiating ESCs and find that SOX2 PTMs are developmentally regulated. In ESCs SOX2 is subject to a poorly understood PTM, the addition of an O-linked N-acetylglucosamine sugar, which is a nutrient responsive modification. Mutational analysis of SOX2 that cannot be modified showed that this PTM regulates the ability of SOX2 to interact with protein partners and controls which regions of the genetic code SOX2 occupies. These studies link a nutrient sensing PTM to pluripotency via regulation of a key pluripotency transcription factor.

Scientific Abstract:
The transcription factor SOX2 is central in establishing and maintaining pluripotency. The processes that modulate SOX2 activity to promote pluripotency are not well understood. Here, we show SOX2 is O-GlcNAc modified in its transactivation domain during reprogramming and in mouse embryonic stem cells (mESCs). Upon induction of differentiation SOX2 O-GlcNAcylation at serine 248 is decreased. Replacing wild type with an O-GlcNAc-deficient SOX2 (S248A) increases reprogramming efficiency. ESCs with O-GlcNAc-deficient SOX2 exhibit alterations in gene expression. This change correlates with altered protein-protein interactions and genomic occupancy of the O-GlcNAc-deficient SOX2 compared to wild type. In addition, SOX2 O-GlcNAcylation impairs the SOX2-PARP1 interaction, which has been shown to regulate ESC self-renewal. These findings show that SOX2 activity is modulated by O-GlcNAc, and provide a novel regulatory mechanism for this crucial pluripotency transcription factor.